Altered Interoception of an Intoxicated State after Administration of Semaglutide

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Introduction

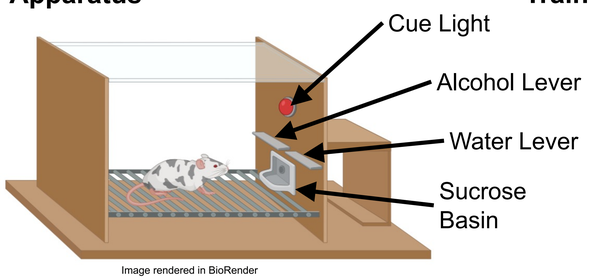
Alcohol use disorder (AUD) is an incredibly prevalent yet debilitating disorder, affecting 10.6% of Americans ages 12 and older as of 2021[1]. Semaglutide, a glucagon-like peptide-1 receptor agonist, is currently being used for type 2 diabetes mellitus patients to aid with weight loss[2,3], but recent studies have analyzed anecdotal evidence from social media platforms and provided evidence of reduced alcohol consumption in people with obesity taking semaglutide[4]. Preclinical studies have shown semaglutide to decrease voluntary intake of alcohol in rats, with some studies concluding that it could have applications for the treatment of AUD[5]. However, there is a lack of research examining interoception under the influence of alcohol while taking semaglutide, which could provide insight into the mechanism of why semaglutide appears to reduce drinking behavior.

This project aimed to explore how semaglutide affects alcohol interoception, or internal perception of the effects of alcohol. Other projects have utilized self-administration procedures and shown that acute use of semaglutide reduces alcohol self-administration behaviors and relapse behaviors[5,6]. This project is unique in the implementation of a discrimination procedure, as the mechanism and cause of this reduced drinking behavior is unknown. Accurate responding would indicate an experience consistent with typical alcohol intoxication, but inaccurate alcohol responses indicate a change in the interoceptive experience.

This project trained rats to discriminate for a reward based on interoception of intoxication by alcohol. Then, rats were exposed to varying doses of semaglutide and administered alcohol, and their discrimination performance was analyzed over multiple tests. Based on existing self-administration literature, we hypothesized decreased accuracy of alcohol discrimination, reflecting a change in interoception of alcohol intoxication when administered semaglutide.

Methods

Apparatus



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Training Curve

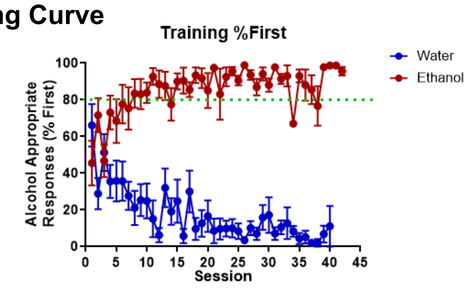
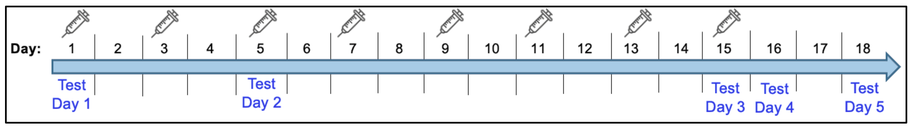


Figure 1. Discrimination training curve of female rats.

Training Timeline

Testing Timeline



Discrimination Procedure

- **Training:** Long Evans rats (6 male, 10 female) were administered either alcohol or water on a given training day and placed in an operant chamber with two levers available
  - One lever gives a sucrose reward when they are intoxicated, and the other lever gives the reward when they are "sober"
  - Training continues until rats consistently use the interoceptive alcohol cue to choose the correct lever
- **Testing**: Rats were started on an every-other-day semaglutide regimen across 15 days, with test days at multiple timepoints to determine whether semaglutide alters alcohol interoception

Chronicity Experiment

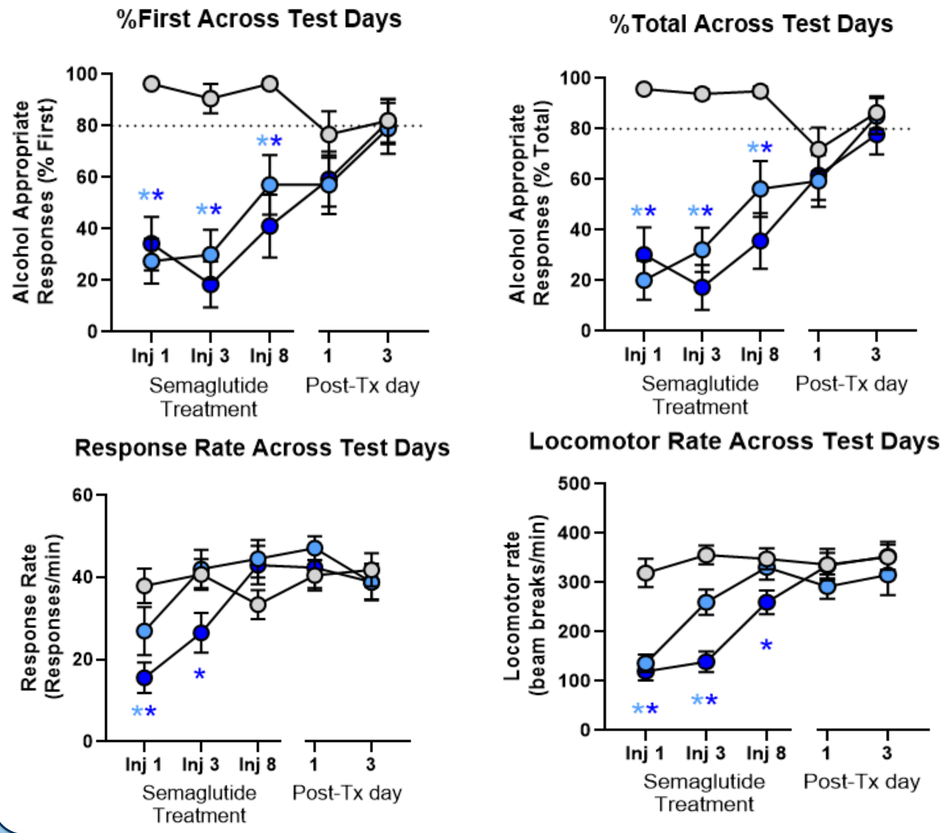


Figure 1. Discrimination behavior data across test days. **(A)** Mean percent of alcohol appropriate responses from first 10 lever responses (%First) across test days at varying doses of semaglutide. **(B)** Mean percent of alcohol appropriate responses from total lever presses (%Total) across test days at varying doses of semaglutide. **(C)** Mean rate of responses per minute across test days at varying doses. **(D)** Mean locomotor rate, using beam disruptions per minute, across test days at varying doses. * $p < 0.05$.

Dosage Experiment

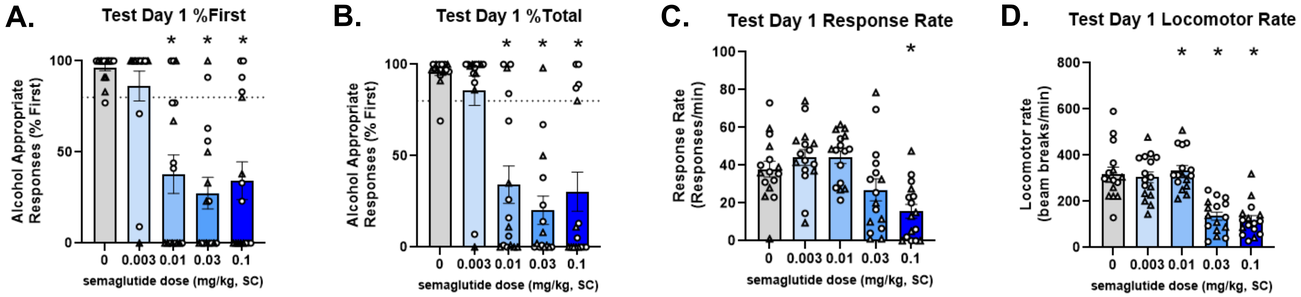


Figure 2. Acute administration of varying doses of semaglutide (A) Mean percent of alcohol appropriate responses from first 10 lever responses on test day 1 (acute dose) at varying doses. **(B)** Mean percent of alcohol appropriate responses from total lever presses on test day 1. **(C)** Mean response rate on test day 1. **(D)** Mean locomotor rate on test day 1. * $p < 0.05$.

Conclusions

- Semaglutide alters interoception of alcohol intoxication in rats both acutely and chronically. The effect diminishes once semaglutide is discontinued or if the dose is lowered enough.
- Specific lower doses may reduce alcohol interoceptive effects with fewer side effects.
- Future work will analyze whether semaglutide affects alcohol metabolism.
- As semaglutide is in clinical trials for treatment of alcohol use disorder, it will be important to examine whether individuals report a change to their intoxication state.

References

View references here:

Acknowledgements

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